The TBC1D15 Oncoprotein Controls Stem Cell Self-Renewal through Destabilization of the Numb-p53 Complex.

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Public Summary:
The molecular mechanisms underpinning the unchecked expansion of highly malignant tumor-initiating stem-like cells are not well understood. Here, we identify TBC1D15 as an oncoprotein that can competitively disengage the p53 tumor suppressor from its protective association with Numb, leading to proteolysis of p53 and to the deregulated propagation of tumor stem cell populations. Upon acute nutrient deprivation, TBC1D15 is subjected to autophagic degradation, thereby linking cellular energy and nutrient status to self-renewal capacity.

Scientific Abstract:
Stem cell populations are maintained through self-renewing divisions in which one daughter cell commits to a specific fate while the other retains the multipotent characteristics of its parent. The p53 tumor suppressor, in conjunction with its interacting partner protein Numb, preserves this asymmetry and functions as a vital barrier against the unchecked expansion of tumor stem cell pools; however, little is known about the biological control of the Numb-p53 interaction. We show here that Numb and p53 are the constituents of a high molecular mass complex, which is disintegrated upon activation of aPKCzeta, a Numb kinase. Using large-scale affinity purification and tandem mass spectrometry, we identify TBC1D15 as a Numb-associated protein and demonstrate that its amino-terminal domain disengages p53 from Numb, triggering p53 proteolysis and promoting self-renewal and pluripotency. Cellular levels of TBC1D15 are diminished upon acute nutrient deprivation through autophagy-mediated degradation, indicating that TBC1D15 serves as a conduit through which cellular metabolic status is linked to self-renewal. The profound deregulation of TBC1D15 expression exhibited in a diverse array of patient tumors underscores its proposed function as an oncoprotein.